

TOBACCO CONTROL

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Editorials

Are tobacco products drugs? Evidence from US Tobacco

In 1499, Amerigo Vespucci recorded the following observations about a custom among the men living on an island off the coast of Venezuela:

Each had his cheeks bulging with a certain green herb which they chewed like cattle, so that they could scarcely speak. And hanging from his neck each carried two dried gourds one of which was full of the very herb he kept in his mouth; the other full of a certain white flour like powdered chalk. Frequently each put a certain small stick (which had been moistened and chewed in his mouth) into the gourd filled with flour. Each then drew it forth and put it in both sides of his cheeks, thus mixing the flour with the herb which their mouths contained. This they did frequently a little at a time.¹

While there is some controversy among historians whether the herb in this particular instance was coca leaf or tobacco, tobacco chewing was common among the native Americans of this region.¹ The white flour used as an additive for both coca leaf and tobacco by these peoples was pulverised shell, which is calcium carbonate. Ashes, which are also alkaline, were used as an additive for tobacco as well. Similar recipes for oral tobacco were common elsewhere in the Americas, and today, small bags of powdered lime are sold in village markets throughout India, southeast Asia, and Indonesia along with the shredded tobacco and other ingredients used to make quids (Prakash Gupta, written communication, 10 January 1995).

More than 50 years ago, Janet Travell and others demonstrated the basic pharmacological principle underlying this practice.^{2,3} Alkaloids such as nicotine and cocaine are rapidly absorbed into the body from alkaline solutions, but their absorption is markedly slower from acidic solutions. In the alkaline state, nicotine and cocaine molecules are mostly un-ionised (the electrically neutral, unprotonated, free base) whereas, in acidic environments, most of them have a positive charge (salts). The relative proportion of each form is a function of the hydrogen ion concentration, which is usually expressed using the inverse logarithmic scale called pH. The neutral forms of cocaine and nicotine pass readily through biological membranes, whereas the charged forms are excluded. (The lung is an exception to this rule, probably because of its vast surface area.)

These principles, understood by pharmacologists since at least 1940, were known to, and used by, scientists at the British-American Tobacco Company in the 1960s.⁴ Indeed, in 1970, scientists employed by the tobacco manufacturers of the UK, working in the Department of Pharmacology of the Tobacco Research Council Laboratories, published the results of experiments on this subject.⁵ Armitage and Turner showed that, at a low pH (6), nicotine was only slowly absorbed from the mouth of

a cat, whereas absorption was rapid at a high pH (8). The authors commented, "the pharmacological response is clearly dependent on the amount of nicotine in the mouth as free base."

The reinforcing qualities of nicotine and other psychoactive drugs such as cocaine are not merely functions of dose. Rather, as discussed by Henningfield and his colleagues elsewhere in this issue, they also involve the rate at which the dose is presented to the brain.^{6,7} The use of different nicotine delivery devices produces different patterns of blood nicotine increase. The more rapidly the nicotine level rises in the blood, the more reinforcing and dependence-producing it is.

In this issue of *Tobacco Control*, Henningfield and his colleagues⁶ and Djordjevic and her colleagues⁸ show for the first time that moist snuff brands vary markedly in their pH levels and hence in their relative proportions of un-ionised, free nicotine. In particular, brands of moist snuff from US Tobacco (UST), the dominant manufacturer of these products in the US, show a wide range of pH and free nicotine values. The pH values observed by Djordjevic ranged from 5.15 (Skoal Bandits) to 8.37 (Copenhagen), which, because pH is a logarithmic scale, spans more than a thousandfold difference in acidity. It is very unlikely that differences as large as these are inadvertent.

Skoal Bandits has a low pH and a very low level of free nicotine, Skoal Long Cut and Skoal Fine Cut have intermediate pH values and free nicotine levels, and Copenhagen has the highest pH and the greatest proportion of free base nicotine among UST brands. These findings indicate that, all other things being equal, the use of Skoal Bandits will produce the slowest rate of increase in blood nicotine level and the use of Copenhagen will produce the most rapid rise among these four brands.

The larger surface area of the more finely cut tobacco shreds in Skoal Fine Cut and Copenhagen may also increase the rates of absorption from these products compared with more coarsely cut products such as Skoal Long Cut.

Studies of the actual blood nicotine levels achieved in human volunteers over time after the administration of these various products have not been reported, so direct evidence that these predicted differences actually occur is lacking. However, the article in this issue by Tomar and his colleagues provides solid indirect evidence that this is, in fact, the case.⁹ Moreover, whether or not more rapid dosing of nicotine occurs with use of brands having the higher levels of free nicotine, the evidence presented by Connolly in this issue indicates that this outcome is, in fact, intended by the manufacturer.¹⁰

Tomar and his colleagues from the US Centers for

Disease Control and Prevention report that, among smokeless tobacco users aged 10–22 years, the use of Skoal and Skoal Bandits declines with increasing duration of use whereas the use of Copenhagen increases. Moreover, users of brands with high free nicotine levels reported having a greater difficulty quitting and more withdrawal symptoms than did users of brands with low or moderate levels of free nicotine.

Connolly documents that UST has had, to use the company's word, a deliberate, specific "graduation" strategy in the marketing of its moist snuff products. Skoal Bandits and Happy Days were designed as starter products, whereas Skoal Long Cut and Skoal Fine Cut represent intermediate stages leading to Copenhagen. Moreover, the objective UST saw these products fulfilling was the provision of what a company official called "nicotine satisfaction" (the pharmacological effects of nicotine on the brain) to the consumer.

The free nicotine levels in UST moist snuff brands precisely match this marketing plan. Moreover, the epidemiological data indicate that the plan has worked: novice customers tend to start with products having lower free nicotine levels and then move to Copenhagen. Copenhagen users feel more addicted than do users of Skoal and Skoal Bandits. This outcome is predicted by the free nicotine levels. UST uses the alkalinising agents sodium carbonate and ammonium carbonate as additives in moist snuff.¹¹ Although UST itself has not said that these additives are used to increase free nicotine levels to enhance nicotine absorption, two other manufacturers of oral nicotine products have openly said that this is precisely the reason sodium carbonate is used in their products. The Swedish Tobacco Company uses sodium carbonate as an additive in moist snuff products for the express purpose of enhancing nicotine absorption.¹² AB Leo puts sodium carbonate into nicotine gum for the same reason.^{13,14} Moreover, Henningfield has reported that UST apparently funded human studies comparing nicotine absorption from cigarettes with that from moist snuff.¹⁵

In the US, the Food, Drug, and Cosmetic Act authorises the Food and Drug Administration (FDA) to regulate drugs. The Act defines "drug" in terms of a manufacturer's intent. One of the definitions is that an article is a drug (as long as it is not a food) if the manufacturer intends that the article affect the structure or function of the body. Any pharmacological action of nicotine, not just the maintenance of addiction, if it is intended by a tobacco product manufacturer, can weigh in the agency's determination of whether a tobacco product is a drug.

The information presented in the four articles in this issue of *Tobacco Control* indicates that moist snuff products produced by UST have a gradient of free nicotine content, and hence potential nicotine bioavailability, that correlates precisely with the company's self-described graduation marketing strategy for introducing new users to moist snuff use and for moving them to products which have, to borrow a term used by a senior UST executive, a greater "kick". Furthermore, UST uses an additive which

another maker of moist snuff indicates it uses to enhance nicotine absorption. The fact that UST uses sodium carbonate in its processes when another manufacturer in the same industry says that the role of sodium carbonate is to enhance the pharmacological activity of nicotine suggests that UST uses this material for the same reason.

Taken together, these four articles speak directly to one of the most important questions now before the Food and Drug Administration¹⁶: are tobacco products drugs? The evidence presented in this issue of *Tobacco Control* helps answer part of this question, the part dealing with moist snuff. Specifically, my conclusion is that the moist snuff products produced by UST are, indeed, intended by the manufacturer to lead to nicotine absorption and to produce nicotine satisfaction in the consumers of these products. That is, UST intends that its moist snuff products affect the function of its customers' bodies, so that these products are, then, drugs. The Food and Drug Administration should therefore assert regulatory authority over moist snuff products, at least over those manufactured by UST.

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